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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,399	07/01/2003	John R. Desjarlais	067461-5097-US01	1891

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

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09/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/611,399	DESJARLAIS ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,20,22-26 and 36-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,20,22-26 and 36-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 21 August 2007 has been entered.

Response to Amendment

Claims 17 and 18 have been amended as requested in the amendment filed on 21 August 2007. Following the amendment, claims 17, 18, 20, 22-26 and 36-45 are pending in the instant application.

Claims 17, 18, 20, 22-26 and 36-45 are under examination in the instant office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicants' response and withdrawn.

Claim Objections

Claim 17 is objected to because of the following informalities: Line 7 contains the typo "and at least one a naturally occurring..."

Furthermore, it is suggested that the acronym "TNFSF" is defined in the first line of the claim.

Appropriate correction is required.

Double Patenting

The provisional obviousness-type double patenting rejection of claims 17, 18, 20, 22-26 and 36-45 as being unpatentable over claims 1-16 of copending application No. 10/963,994 is maintained for reasons of record.

The provisional obviousness-type double patenting rejection of claims 17, 18, 20, 22-26 and 36-45 as being unpatentable over claims 1-16 of copending application No. 11/008,091 is maintained for reasons of record.

The provisional obviousness-type double patenting rejection of claims 17, 18, 20, 22-26 and 36-45 as being unpatentable over claims 18, 23-26, 33, 36, 37, 39-41, 43 and 44 of copending application No. 10/338,083 is maintained for reasons of record.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, 20, 22-26 and 36-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for variant TNFSF proteins

that physically interact with a corresponding TNFSF protein and for a variant TNFSF protein that physically interacts with a non-corresponding naturally occurring TNFSF protein consisting only of the combination of Blys and APRIL and a mixed oligomer thereof, does not reasonably provide enablement for any variant TNFSF protein that physically interacts with a non-corresponding naturally occurring TNFSF protein or mixed oligomer(s) thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are drawn to variant TNFSF monomer proteins and mixed TNFSF oligomers comprising at least one variant TNFSF protein and a naturally occurring TNFSF protein. It is noted that although claims 17, 18, 20, 22-25 and 36-45 do not explicitly recite that the variant TNFSF proteins physically interact with a non-corresponding naturally occurring TNFSF protein as in claim 26, all of the pending claims encompass this limitation. This is because the claims recite the open language "comprising," which does not exclude additional unrecited elements (see MPEP 2111.03).

In the reply filed 21 August 2007, Applicants assert, "TNFSF members do not exchange with each other to form dominate negative heterotrimers. Attached as Exhibit A is the recent article 'Dominant-Negative Inhibitors of Soluble TNF Attenuate Experimental Arthritis without Suppressing Innate Immunity to Infection' by Zalevsky et al., J IMMUNOL. 2007 Aug 1;179(3):1872-83. (Dr. Zalevsky and many of other authors are current or former employees of Xencor, Inc., the assignee of the present application.) As shown in Figure 1 and the first full paragraph of page 1876, TNF-alpha does not exchange with TNF-beta (also called lymphotoxin α) the most closely related cytokine to TNF-alpha to form dominate-negative heterotrimers. Specifically: Because many proteins in the TNF superfamily share conserved structural features, it was important to determine whether the exchange mechanism of DN-TNF is specific for [TNFα]; therefore, a signaling assay was established to measure inhibition of lymphotoxin α [soluble-TNFβ], the most closely related cytokine. As described above, the three classes of TNF inhibitors blocked recombinant mouse solTNF (Fig. 1B). However, DN-TNF and [antibody] failed to block recombinant mouse lymphotoxin α (each with a > 1000-fold loss of potency relative to solTNF), while the decoy receptor retained activity (Fig. 1E), in agreement with a previous report (26). Taken together, the five studies shown in Fig. 1 demonstrate that DN-TNF biologics effectively antagonize recombinant or endogenously produced solTNF with comparable overall efficacy to a decoy receptor and anti-TNF Abs; however, DN-TNF does not block the activity of lymphotoxin α. Thus, since DN-TNF α does not exchange and block activity of its most closely related cytokine, lymphotoxin α, there is no reason to assume the less related

TNFγ will do so. Applicants respectfully submit that wild-type TNFSF members do not exchange with each other *in vivo* to create dominant-negative heterotrimers" [Emphasis added]. Applicants further assert, "BLyS and APRIL, two members of the TNFSF, appear to exchange to form biologically active heterotrimers. Attached, as Exhibit B, is the article 'BLyS and APRIL Form Biologically Active Heterotrimers That Are Expressed in Patients with Systemic Immune-Based Rheumatic Diseases,' by Roschke et al., J IMMUNOL. 2002 Oct 15;169(8):4314-21. As the title states, and the results support, any BLyS/APRIL heterotrimers are biologically active, meaning they cause receptor signaling, and are thus outside the scope of the present claims. Again, Applications are not aware of any wild-type TNFSF member which will exchange with any other TNFSF member *in vivo* to form a dominant-negative heterotrimer." [Emphasis added].

Thus, according to Applicants' arguments as well as the prior art, variant TNFSF proteins will only interact with the corresponding wild-type protein to form mixed trimers, (e.g., DN-TNF-α will only interact with wild-type TNF- α), with one exception. That is, Blys and APRIL appear to be able to interact. Applicants' specification supports this contention, as the examples on pp.45-55 are drawn to studies involving DN-TNF-α associating with wild-type TNF-α and DN-RANKL associating with wild-type RANKL. Further, the specification at p. 56 teaches "BlyS, CD40L, APRIL, OX-40 are generated according to the protocol disclosed above. They have exchange with their corresponding wild-type TNFSF member. APRIL and BlyS have exchange between them and the corresponding APRIL or BlyS."

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Given the lack of direction/guidance presented in the specification, the absence of working examples, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claimed methods, and the breadth of the claims which encompass any variant TNFSF protein that physically interacts with a non-corresponding naturally occurring TNFSF protein or mixed oligomer(s) thereof, undue experimentation would be required of the skilled artisan to practice the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 18, 20, 22-25 and 36-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Loetscher et al. (J Biol Chem. 1993 Dec 15;268(35):26350-7).

The claims are drawn to variant TNFSF monomer proteins and mixed TNFSF oligomers comprising at least one variant TNFSF protein and a naturally occurring TNFSF protein.

The Loetscher et al. reference teaches mutated TNF-α proteins, which were analyzed for selective binding to recombinant 55- and 75-kDa TNF receptors in

competition with radiolabeled wild-type TNF-α. The reference teaches that mutations in the loop from position 29 to 34 and at positions 86 and 146 preferentially impaired binding to the 75-kDa TNF receptor, whereas mutations in the region from 143 to 145 mainly affected binding to the 55-kDa TNF receptor. The reference also teaches that mutation of the conserved Tyr87 resulted in a dramatic loss of binding activity to both receptors. The reference teaches that selectivity for one or the other receptor type was enhanced by combining two or three point mutations, the effects of the single mutations with respect to receptor selectivity being at least additive (entire document; e.g., abstract). The Loetscher et al. reference also teaches that the mutants assembled into trimers (p.26352, col.2, fourth paragraph under Results). Given that the reference teaches the substitutions recited by the instant claims, the reference inherently teaches that the variants assemble into mixed trimers (comprising naturally-occurring proteins and non-naturally occurring variants) and antagonize soluble naturally occurring TNFSF proteins, thus meeting the limitations of claims 17, 18, 20, 22, 24, 25 and 44. The reference teaches that the substitutions are at receptor contact positions (p.26351, col.1), thus meeting the limitations of claim 23, and teaches surface substitutions (p.26352, col.1, first paragraph under Results), thus meeting the limitations of claim 37. In addition, the reference teaches non-conservative substitutions (e.g., p.26353, Table 1) at the residues mentioned above, thus meeting the limitations of claims 36, 38, 39 and 41-43. The Loetscher et al. reference also teaches mutants with substitutions at residues 65-76 (p.26352, col.2, third paragraph under Results), thus meeting the limitations of claim 40, and teaches the mutants contained in a pharmaceutically

acceptable carrier (phosphate buffered saline: p.26351, col.2, under Purification of Human TNFα Mutants), thus meeting the limitations of claim 45.

Since the reference teaches all the limitations of the claims, claims 17, 18, 20, 22-25 and 36-45 are anticipated by Loetscher et al.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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19 September 2007

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